

## **CHAPTER II: HERBS AND OTHER DIETARY SUPPLEMENTS**

### **Research Highlights**

I'm going to give you a couple of highlights of what we do in order to address those needs. We, along with the National Center for Complementary and Alternative Medicine (NCCAM), fund a series of high-end, multidisciplinary, botanical research centers around the country. Their tasks are broad. They're expected to identify and characterize the botanicals that they're using, to assess some elements of their physiology, chemistry, and mechanism of action, and then to begin some early clinical evaluations. These are ambitious and tough charges to be giving to organizations, and it's probably one of the reasons why there are only 6 of them in our stable. Along with our partners at the NIH, we also fund research on a variety of topics, and I've just given some examples of recent ones here.

The action of folic acid is mediated by a receptor, and one of the important reasons for taking folate before and during pregnancy is that it can reduce the incidence of major craniofacial malformations in fetuses. We, in the National Institute of Dental and Craniofacial Research at the NIH, embarked on funding a series of studies in this area.

Chromium has been implied as being potentially valuable in the management of diabetes, and so we fund research with the National Institute of Diabetes and Digestive and Kidney Diseases to look at the effect of chromium on insulin action.

The list goes on: B vitamins; St. John's wort; conjugated linoleic acid, which has been touted for its possible use in weight management; and S-adenosyl-L-methionine, which is very enthusiastically supported for its role in a number of things. There are some very promising uses for S-adenosyl-L-methionine. Likewise for omega-3 fatty acids. We also embark on some very basic studies with our partners, so just developing methods for the analysis of these things is an area where there needs to be more work than is currently going on.

We use an evidence-based approach in order to help us to identify the areas, particularly sensitive areas, where further research is necessary. A program like this is not unlike the kind of program that is used in evidence-based medicine. The tools of evidence-based medicine, systematic review of the literature, meta-analysis, and other tools as appropriate, are brought to bear on issues related to dietary supplement efficacy and safety. Although the approach of evidence-based medicine is used for lots of different kinds of reasons, we have a very special set of reasons ourselves, and that is for the purpose of assisting us in identifying and developing the next appropriate steps in a research agenda.

I'm going to give you 2 examples of ones that we've done. This is the first one that we did. Here is another very handsome picture of ephedra sinica, which is used for the purposes of weight management and athletic performance enhancement. Ephedra is widely used, and until recently, its sales were enormous. Of all of the dietary supplement sales in the U.S., it is said that ephedra-containing products accounted for between \$2 and \$3 billion of sales. It was primarily for the purposes of enhancing athletic performance and weight management. There were believed to be some encouraging signs, often from the literature, associated with purified ephedrine, which is one of the alkaloids that's present in ephedra. But how much work had really been done on the herb ephedra for these purposes? So through a collaboration with our partners, the Agency for Healthcare Research and Quality and Evidence-Based Practice Centers, the RAND Evidence-Based Practice Center in Southern California was asked to do a review that included relevant reports on this topic in all languages, and to the extent possible, to not only cull the published literature but also the unpublished literature. As is often the case in the dietary supplement world, there's a lot of unpublished information or information in other languages. Marketing of supplements in this country is sometimes based on that borrowed science. It doesn't mean that it's not good, but it means that it may not have always been evaluated according to the customary rules of evidence that we use in evidence-based medicine. You might have heard of a report that was released in February and published in the *Journal of the American Medical Association* in March; it

occurred just around the same time and was part of the file that the U.S. Food and Drug Administration (FDA) used to exert some more control on ephedra-containing products within the last couple of months. The study reported that ephedra-containing dietary supplement products had demonstrated positive modest effects on weight in the short term, but there was actually no evidence of an effect of ephedra on athletic performance enhancement. It doesn't mean that there isn't one, but it means that there was no systematically developed evidence in support of it. Likewise, there were some side effects that were seen in these trials, the few trials that were done in weight loss. But at the same time, some very serious adverse events had been filed with the FDA and at least one major ephedra manufacturer. But it's very difficult to prove cause and effect—for example, that ephedra caused heart attack, psychosis, or stroke—because too often the smoking gun is not there. But at the end of the day, a consumer is left with the dilemma. Does it work, does it not work? Is it safe, is it not safe? We're still left with some tantalizing information that ephedra may be effective, at least in weight management, but there really has not been enough work done on either efficacy or safety in order for me to advise you. I wouldn't anyway, but I don't have enough information upon which to give you advice. In my own case, I would avoid taking ephedra-containing products because I don't have a sufficient amount of confidence that the product, as marketed, is safe for use. But that's me. What's happened in the meantime is quite interesting. The Internet, as you know, is a big tool for marketing dietary supplement ingredients, and so here's a product called Suddenly Slim, and it contains ephedra. You don't have to go very far to find other ephedra-related Web sites. Here's one for an ephedra attorney who asks if you have been injured by ephedra. What that ends up leading to is another product, Suddenly Slim Free, which is now ephedra-free. It's the same product as the other except now it has something else in it that replaces the ephedra that was there for its putative weight management effects. One of the interesting things about this, of course, is what the manufacturer did when it took ephedra out of the product. Did it put something else in? It's likely that if there was not much work done on the ephedra part of this product, there may not have been much work done on the other non-ephedra parts of the product either. Be cautious.

Here's a much more enjoyable story to tell. Omega-3 fatty acids are touted for their potential value in a number of situations: preventing heart disease or reducing risk of heart disease; reducing risk for cancer; improving bone health; enhancing immune function; improving cognition; and reducing depression. There are a number of putative actions of omega-3 fatty acids. One of the first things that needs to be done is to determine whether the beneficial impact of omega-3 fatty acids for any of these situations derive from them being in food or in dietary supplements. So any time a question is raised about the utility of a dietary supplement ingredient, one of the first things that occurs to me is whether or not the value is related to it being in food or in supplements. The question is then tractable. It's something that you can study, but you have to think to study that sort of thing. As part of our second ambitious foray into the evidence-based field, we commissioned a systematic review of the literature with all of the meta-analytic and other tools, as appropriate, on omega-3 fatty acid supplementation for a number of health indications — prevention of heart disease, immune function enhancement, mental health, and others. Out of this collection of questions, a series of evidence reports, much like the one that was published on ephedra recently, will be developed over the next couple of years. Again, the reason for doing this is to assist us and our partners at the NIH, notably the National Heart, Lung, and Blood Institute but many others as well, in the development of an appropriate research agenda that will address future questions. It's quite possible that the science is far enough advanced on omega-3 fatty acids and its role in prevention of heart disease that we're ready for a public health recommendation. I personally think that there are some steps in between before an organization as conservative as the government—and you'd want them to be conservative in something like this—would want to make a statement that omega-3 fatty acids have a positive ameliorating effect on your risk for heart disease and that you should go out and eat lots of fish or you should go out and take lots of supplements. I think the answer is probably a little safer with the former than with the latter simply because the data are not in yet. We don't know enough about the use of supplements for this purpose. But there's a lot of promise there.